Clinico-pathological Features of Liver Metastases from Colorectal Cancer in Relation to Prognosis

AUTHOR(S):

MORINO, TAKAHARU; TANAKA, JUNJI; TOBE, TAKAYOSHI

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Clinico-pathological Features of Liver Metastases from Colorectal Cancer in Relation to Prognosis

Takaharu Morino, Junji Tanaka, Takayoshi Tobe

The 1st Department of Surgery, Faculty of Medicine, Kyoto University
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Abstract

Twenty-nine patients undergoing hepatic resection for colorectal metastases from 1980 to 1986 were studied. The overall cumulative survival rates were 82%, 63% and 32% at 1, 2 and 3 years, respectively. The possible prognostic factors, i.e., Dukes' staging of the primary lesion, the number of metastatic nodes, synchronous versus metachronous appearance of metastases, and curative versus non-curative resection were estimated. Evaluation of those categories did not provide any significant information for prognosis after hepatic resection for liver metastases. The growth patterns of the tumor boundary were classified into three types as sinusoidal, expansive, and mixed. There was no significant difference in the survival rates among these groups. The significant factor affecting prognosis was only whether the secondary tumors were encapsulated or not. Patients with encapsulated tumor of the interval longer than 2 years between colon resection and hepatic resection had a significantly better survival rate.

Introduction

Liver metastases are present in 25% of patients at the time of initial colorectal cancer resection[24] and will metachronously appear in 50% of patients. The number of resectable liver metastases are now increasing with the recent development of imaging modalities making early diagnosis of secondary hepatic lesions from colorectal cancer possible. It is generally accepted that hepatic resection for liver metastases from colorectal cancer is one of the most effective treatments[13]. However, it remains unclear which clinico-pathological features determine the prognosis after hepatic resection. Previously, Dukes' staging of the primary lesion, the number of metastatic nodes, synchronous versus metachronous appearance of metastases, curative versus non-curative resection, as well as several others have been proposed as possible prognostic factor determinant in such patients[1,5,10,13]. However, these factors remain controversial and are not conclusive. In turn, some investigators have suggested the importance of the biological status rather than the clinical features[24], in regard to postoperative survival. There are no reports concerning a relationship between histological features and prognosis. The present study attempted to clarify the prognostic factors in

Key words: Liver metastases, Colorectal cancer, Prognosis, Growth pattern, Capsule formation.
索引語：肝転移，大腸癌，予後，進展様式，被膜形成．
Present address: First Department of Surgery, Kyoto University Hospital, Sakyo-ku, Kyoto 606, Japan.

regard to clinico-pathology through analysis of postoperative follow-up.

Patients and Methods

Twenty-nine patients with liver metastases from colorectal cancer underwent hepatic resection from 1980 to 1986 at the lst Department of Surgery, Kyoto University Hospital. All of these patients were considered to have had a curative resection of the primary tumor according the General Rules for the Clinical and Pathological Study of Colorectal cancer[15]. Twenty nine specimens were available for pathological study. The group included 16 men and 13 women. The ages ranged from 44 to 82 years with a median age of 64 years. The location of the primary tumors in the 29 patients are summarized in Table 1. Four patients had primaries in the right colon (all synchronous), 8 in the left colon (2 synchronous, 6 metachronous), and 17 in the rectum (5 synchronous, 12 metachronous). The macroscopic findings of the primary lesion according to Borrman's classification showed one patient with Borrman I, 14 with Borrman II, 8 with Borrman III, and none with Borrman IV The remaining 6 patients were unknown. Twelve patients had tumor sizes less than 5 cm in length and 9 were greater than 5 cm, with 8 not measured. Dukes' staging of the primary colorectal cancer revealed one patient with Dukes' A, 9 with Dukes' B, and 15 with Dukes' C. The Dukes' classification of the remaining 4 patients were unknown. The majority of the primary tumors, 18 of 29 patients (62%), were histologically well differentiated adenocarcinomas. Only 8 of 29 patients (28%) had moderately or poorly differentiated adenocarcinomas. There were a total of 14 patients with a solitary hepatic nodule (3 synchronous, 11 metachronous) and 15 with multiple hepatic nodules (8 synchronous, 7 metachronous) (Table 2). Surgical resections consisted of 9 pa-

Table 1

	Synchronous	Metachronous
Solitary tumor	3	11
Multiple tumor		
2	4	3
3	1	3
4–	3	1

Table 2

	Synchronous	Metachronous	Total
Localization			
Caecum	2	0	2
Ascending colon	2	0	2
Transverse c.	0	0	0
Descending c.	0	0	0
Sigmoid c.	2	6	8
Rectum Rs	3	3	6
Rab	2	9	11
Total	11	18	29
Borrman I	0	1	1
II	5	9	14
III	5	3	8
IV	0	0	0
V	1	0	1
unknown		5	5
Size under 5 cm	3	9	12
over 5 cm	6	3	9
unknown	2	6	8
Dukes' A	0	1	1
B	5	4	9
C	6	9	15
unknown		4	4
Histology			
Well differentiated	8	10	18
Moderately diff.	2	4	6
Poorly diff.	0	2	2
others or unknown	1	2	3

tients with wedge resection, 3 with segmentectomy, and 17 with a lobectomy or greater resection. Major hepatic resection, i.e., segmentectomy, lobectomy and extended lobectomy with surgical margins free of tumor were considred to be curative resections. However, all resections involving trisegmentectomy combined with wedge resection for multiple nodes were considered to be non-curative. Based on these parameters, 16 patients underwent successful curative operation, and the remaining 13 patients underwent non-curative operation. Resected specimens from 28 of the 29 pa-

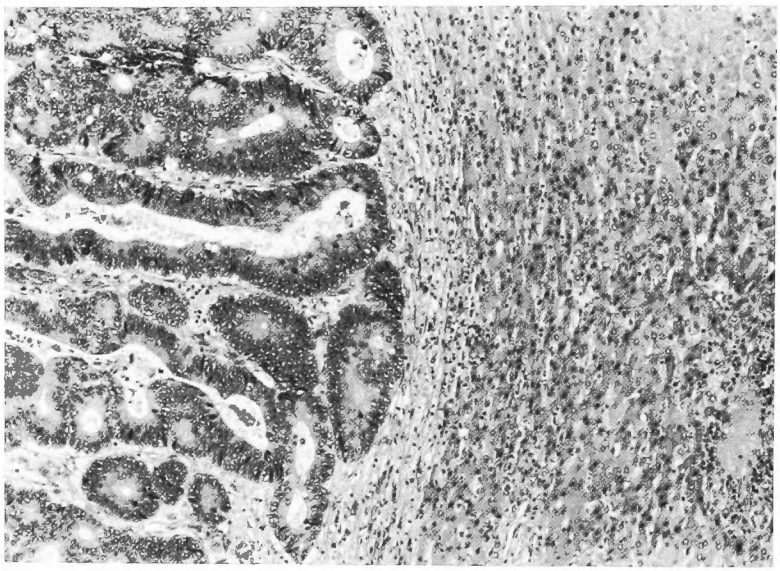

Fig. 1-A. "Expansive" growth pattern. Note that the cancer cells compress the hepatocytes along the liver cell cord.

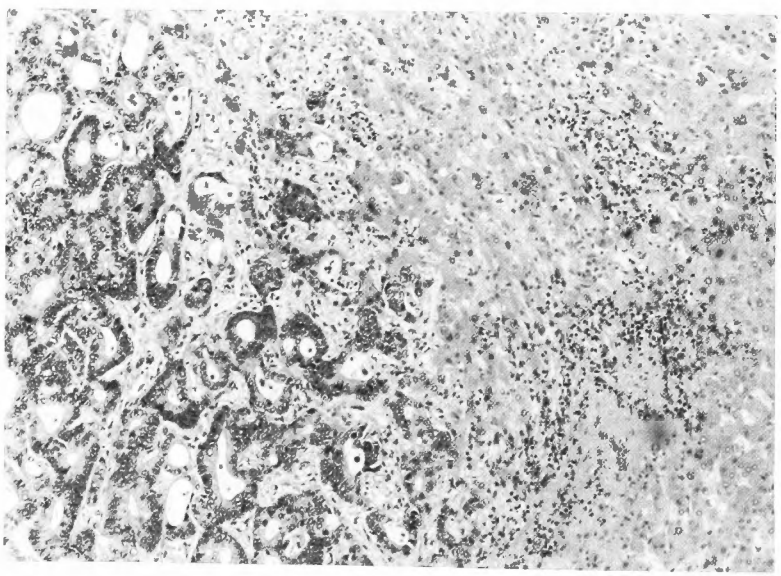

Fig. 1-B. "Sinusoidal" growth pattern of metastatic liver tumor at the tumor boundary. Note that tumor cells invade between the sinusoids.

Fig. 1-C. Macroscopic picture of metastatic liver tumor with capsule formation.

tients were available for microscopic study. These were stained with Hematoxylin-Eosin and Azan-Mallory in order to investigate the growth pattern of the tumor at the tumor boundary, as well as the formation of a fibrous capsule. We classified the tumor growth pattern into three types according to Nakashima's classification[20] as follows; (1) Sinusoidal type: The cancer cells invade the sinusoids and destroy the normal hepatocytes. (Fig. 1–A) (2) Expansive type: The cancer cells are seen compressing the hepatocytes along the liver cell cord. There is no destruction of peripheral hepatocytes. (Fig. 1–B) (3) Mixed type: Some lesions are recognized as sinusoidal and some are expansive type. According to these definitions, 10 patients displayed a sinusoidal growth pattern, 6 had an expansive pattern and 12 had a mixed pattern. Capsule formation, as commonly seen in primary hepatocellular carcinoma, was also observed in the metastatic liver tumors, as demonstrated in Fig. 1–C. Capsule formation was observed in 8 patients. In the present study, causes of death are due to recurrence of cancer. Cumulative rate was calculated according to the method of Kaplan-Meier and statistical significance was determined when the p value was less than 0.05, as estimated by the Wilcoxon test.

Result

There was no 30 day operative mortality or hospital deaths among these patients following hepatic resection for colorectal metastases. Fig. 2 indicates the overall survival rate after hepatic resection for liver metastases. The actual survival rates were 82%, 63% and 32% at 1, 2 and 3 years, respectively. The survival rates were further analyzed according to the following categories. The survival rate with regard to Dukes' staging of the primary lesion is demonstrated in Fig. 3. The survival rate in the Dukes' B group was greater than that of the Dukes' C group, but not significantly. A similar tendency was also observed in curative versus non-curative resection (Fig. 4), synchronous versus metachronous appearance of metastases (Fig. 5), and solitary versus multiple

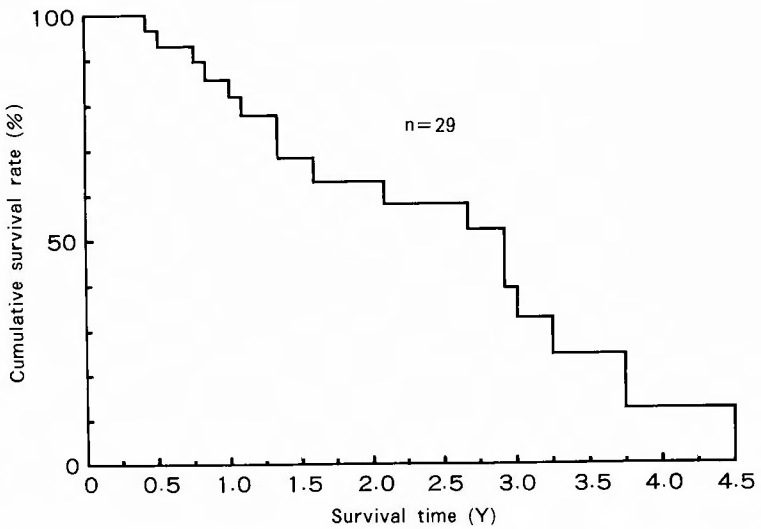

Fig. 2. Postoperative cumulative survival rate following hepatic resection for the secondary lesion.

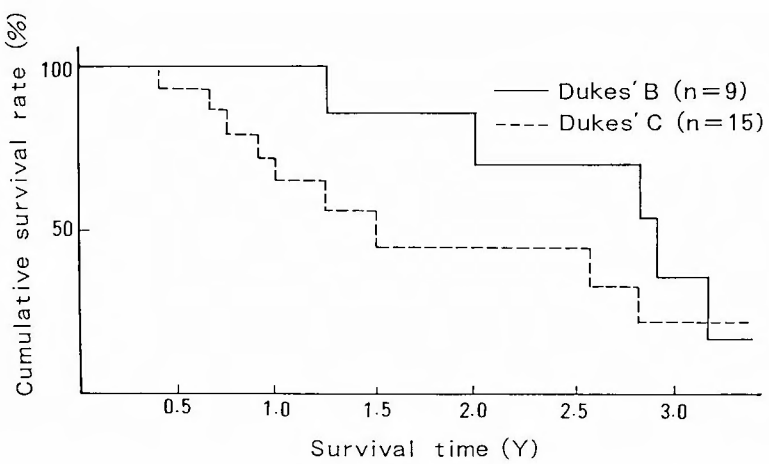

Fig. 3. Postoperative cumulative survival rate according to the stage of primary lesion following hepatic resection. Staging of primary lesions is according to Dukes' classification.

hepatic nodes (Fig. 6). Evaluation of these categories did not provide any significant information for determining the prognosis after hpetic resection for liver metastases from colorectal cancer. Fig. 7 demonstrates the survival rates according to the tumor growth pattern, as defined in "Patients and Methods" Although the numbers in each group are small, there was no measurable difference between these groups. On the other hand, Fig. 8 illustrates the survival rate in regard to capsule formation. The patients with encapsulated liver metastases had a significantly better prognosis than those without encapsulation at 2 years (85% vs. 50%, $p<0.03$) and 3 years (80% vs. 15%, $p<0.01$). Thus, since capsule formation seemed to play a major role in determining survival following hepatic resection for metastases from colorectal cancer, capsule formation was further analyzed in regard to the time interval between the initial and the secondary operations in the metachronous patients.

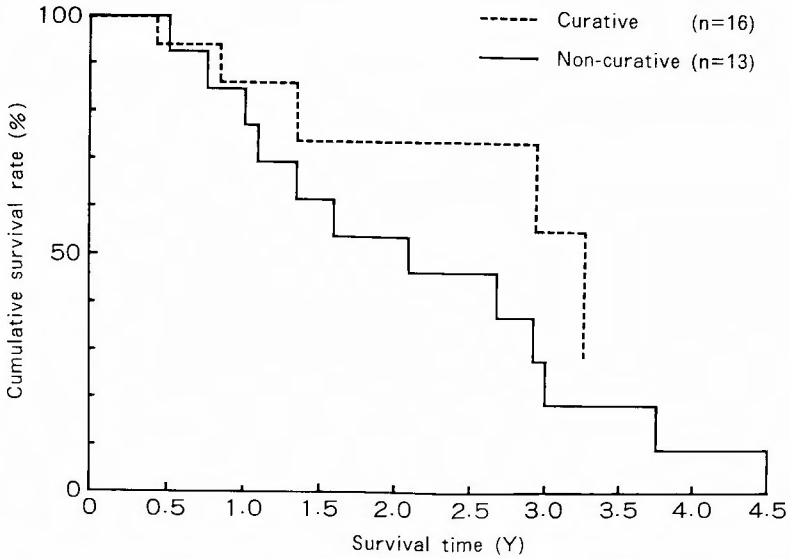

Fig. 4. Cumulative survival rate according to curability for the secondary lesion. The definition of curability is referred to "patients and methods"

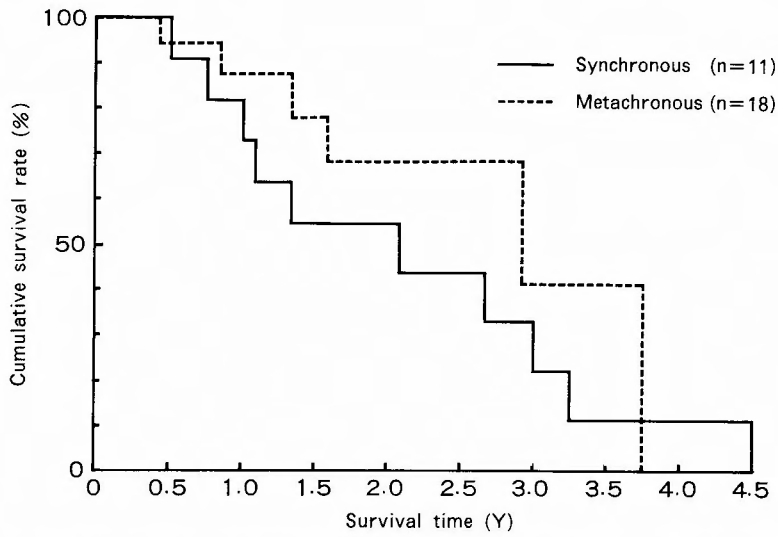

Fig. 5. Cumulative survival rate according to synchronous or metachronous of the secondary lesion.

Each patient with capsule formation had a relatively long interval between the initial operation and the second, that is, 4 of 5 patients with capsule formation had an interval of greater than 2 years before the second operation. Interestingly, capsule formation was also seen in 3 of 11 synchronous patients, as demonstrated in Fig. 9. Fig. 10 illustrates the survival time of each patient in relation to the time interval between the initial and second operation. The survival time was similar between synchronous and metachronous patients whose second operations were performed within 2 years. In contrast, almost all metachronous patients with their second operation longer than 2 years after the initial operation remain alive.

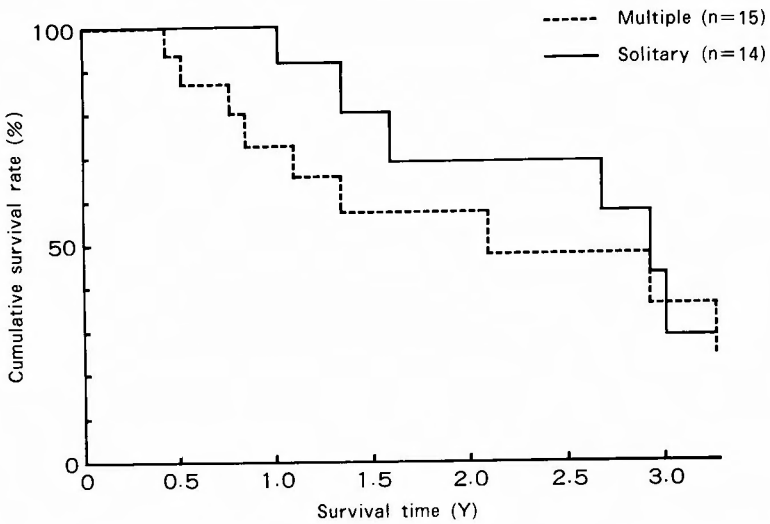

Fig. 6. Cumulative survival rate according to multiple or solitary secondary lesions.

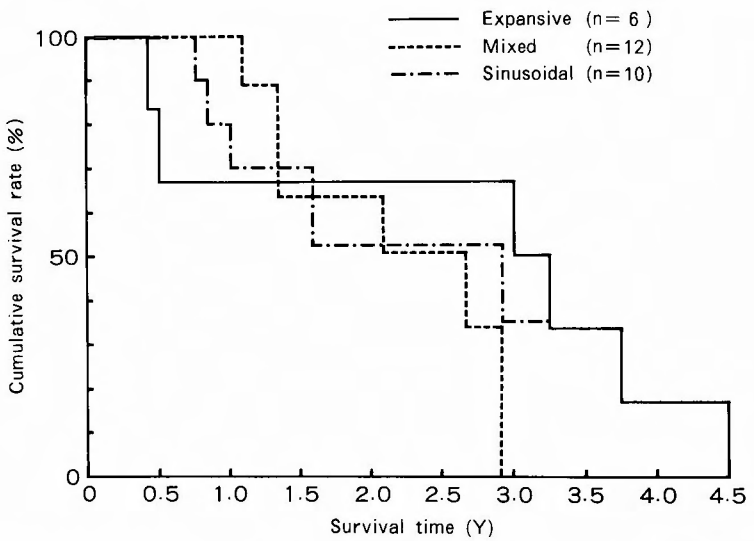

Fig. 7. Cumulative survival rate according to the tumor growth pattern. The definition of "expansive", "mixed" or "sinusoidal" is referred to the "Patients and Methods"

Discussion

Improvements in operative technique, as well as improved perioperative management have resulted in an oeperative mortality rate of 0 to 10%[8,21]. Similarly, we had no operative deaths in the present series. Because of this low mortality rate for hepatic resection of liver metastases, hepatic resection has begun to be considered the procedure of selected choice for hepatic metastases from colorectal cancer. In spite of increasing numbers of hepatic resections, the prognostic factors for liver

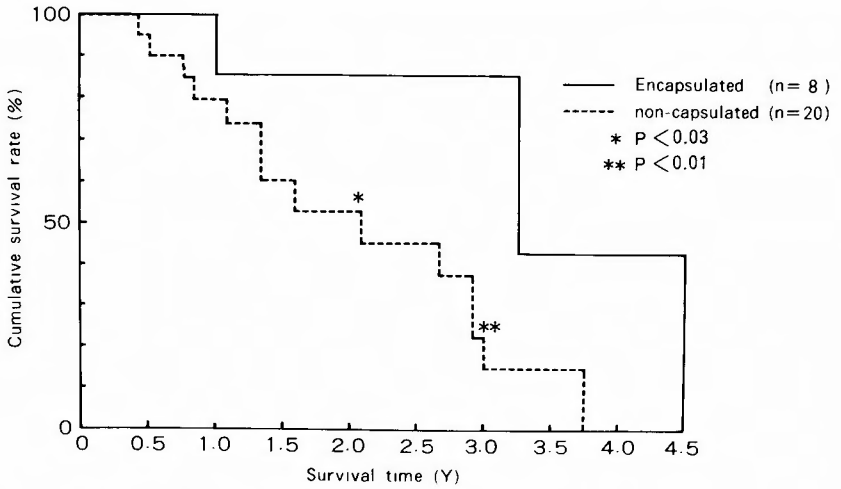

Fig. 8. Cumulative survival rate according to the capsule formation.
* ; $p<0.03$
**; $p<0.01$

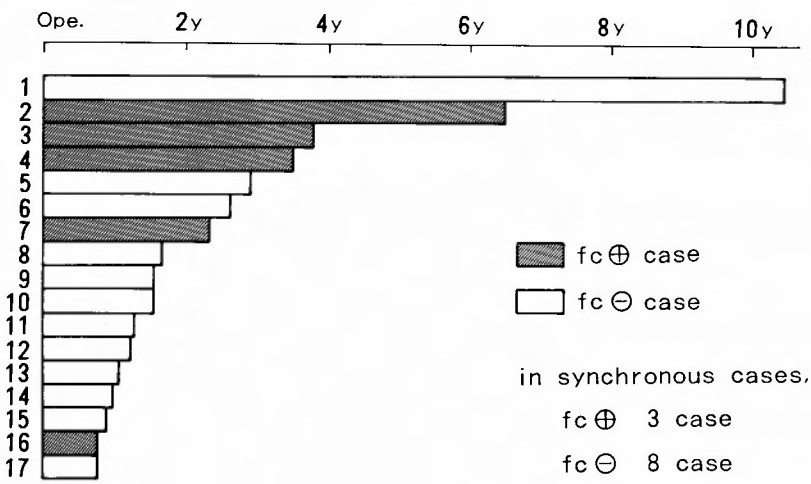

Fig. 9. Time interval between the initial and the second operations in metachronous cases in relation to capsule formation.
fc (+) or (−); capsule formation (+) or (−)

metastases from colorectal cancer after surgery remain controversial and are not definitive. In this study, the overall cumulative survival rates were 82%, 63%, and 32% at 1, 2 and 3 years, respectively. Hepatic resection for metastatic liver tumors are successfully exhibiting a better prognosis when compared with the natural history of the disease[3,4,22,29]. The number of metastatic nodes is considered to be one of the possible factors which influence survival after hepatic resection. Many studies[1,10,25,28] have shown that patients with solitary tumors have a better prognosis than those with multiple tumors. Cady et al.[7] and August et al.[12] indicated that the patients who developed the secondary within three hepatic nodes had a better prognosis. Others[18,27] indicated a better pro-

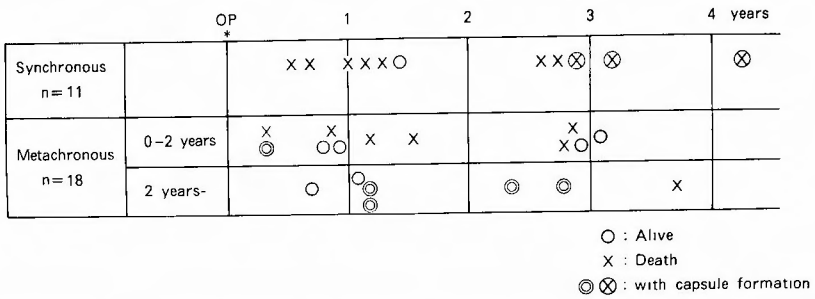

Fig. 10. Actual survival time of each patient in relation to the time interval between the initial and the second operation.
0–2 years or 2 years- indicate less or more than 2 years between the initial and the second operation.

gnosis within four metastatic nodes. In this series, we found no significant difference between these two groups, as did some previous studies[6,8,26]. It is surgically important whether a curative or non-curative operation can improve the postoperative prognosis. There remains some controversy on this topic[5,13]. In our series, there were no significant differences between curative and non-curative operation, which is similar to Olak's report[22]. In addition, a high recurrence rate after hepatic resection has been reported by various investigators in spite of a curative operation initially being performed. Iwatsuki et al.[14] have reported that the pattern of tumor recurrence after hepatic resection appears to be systemic rather than hepatic. This may explain our poor results (survival rate was 32% at 3 years) in comparison to those in other institutes (50% around there at 3 years), taking into consideration that Dukes' staging indicates the extent of the primary which may represent blood borne metastases since Dukes' C had a lower survival rate than did Dukes' B in this study, although the difference was not statistically significant. These results may support the use of perioperative adjuvant therapy in addition to the hepatic resection, for example, using intraportal or intaperitoneal injection of anticancer agents through the implantable pump[7,22,25]. Although the number of controlled study cases are limited, Kemeny et al.[16] reported an improvement in postoperative survival of patients undergoing hepatic resection plus using a pump for adjuvant therapy. Multimodality therapy including chemo-, immuno- and hyperthermic-therapy may be necessary in future.

There are few reports concerning a relationship between histological features and prognosis. In the present study, we classified the tumor growth pattern at the tumor boundary into three types, as described in "Methods" Typical features of these classifications are shown in Figs. 1-A and 1-B. Although the sinusoidal type appears invasive and therefore evoking a poor prognosis, and the expansive type as evoking a good prognosis, the actual results were not expected. Namely, there was no significant difference in the survival rates among the "sinusoidal", "expansive" or "mixed" groups. This methods of classification does not reflect a grading of the malignancy.

In this study, the significant factor affecting prognosis was only whether the secondary tumors were encapsulated. Although it is well known that most hepatocellular carcinomas in Asia are encapsulated by fibrous tissue, there have been no reports concerning capsule formation in metastatic colorectal cancer, particularly in regard to the prognosis. In this series, patients with encapsulated tumor had a significantly better survival rate, in spite of limited numbers. In view of clinicopathology, it is noteworthy that 4 of 7 patients with encapsulated tumors had a time interval greater than 2 years between colon resection and hepatic resection. In this study, as demonstrated in Fig. 9,

our patients with secondary lesions appearing more than 2 years after the primary colorectal resection appeared to have a better prognosis. As a consequence, the time interval between the primary and the secendary carcinomas seems to be an important determinant of prognosis[19,28]. However, there are many other results[2,9,11,17] indicating that the time interval does not influence the postoperative prognosis. On the one hand, almost all metachronous encapsulated lesions appeared more than 2 years after the primary operation. On the other hand, the encapsulated lesions were also seen in synchronous liver tumors, and those patients had a good prognosis, as indicated in Fig. 8. This probably indicates that it is difficult to assume how long the liver metastasis coexisted with the primary colorectal cancer. It is suggested that tumor doubling time may play a role in the mechanism of capsule formation. Also, this result strongly suggests that the biological characteristics of the cancer and natural defense mechanisms seem to be important. In conclusion, capsule formation may be indicative of a good prognosis in hepatic resection of liver metastases from colorectal cancer.

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和文抄録

大腸癌肝転移症例の臨床病理学的検討

京都大学第一外科
森野 高晴，田中 純次，戸部 隆吉

京都大学第一外科で，1980–1986年において，原発巣が治癒切除されたものの，肝転移のため，肝切除を余儀なくされた大腸癌29症例につき，その予後因子につき検討した．累積生存率は1年82%，2年63%，3年32%であった．

原発巣の Dukes 分類，肝転移巣の数，同時性–異時性転移の別，治癒–非治癒肝切除の別による統計学的な差は認められなかった．切除された肝転移巣を病理学的に検索し，腫瘍–非腫瘍境界における発育形式を浸潤型，圧排型，混合型の3型に分類したが，生存率に差を認めることができなかった．転移性肝癌であっても8症例に被膜形成傾向を認め，これらの生存率は，被膜形成のない症例との間で，2年 (85% vs 50%, $p<0.03$) 3年 (80% vs 15%, $p<0.01$) で，統計学的に有意に良好であった．被膜形成を伴う症例の多くは原発巣切除後2年以上を経過し転移巣を形成しており，腫瘍の生物学的特性，特に成長速度と宿主側の防御機能との関連が示唆された．